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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
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DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/380,377	Applicant(s) Bulleid, N.J.
	Examiner Joseph Woitach	Group Art Unit 1632

X Responsive to communication(s) filed on *May 22, 2000* .

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *1-28* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

X Claim(s) *1-28* is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

X Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

X All Some* None of the CERTIFIED copies of the priority documents have been

X received.

received in Application No. (Series Code/Serial Number) _____ .

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

DETAILED ACTION

The amendment filed June 1, 2000 (paper number 13) has been received and entered. The sequence listing has been entered into the specification and the CRF is in compliance. The amendment filed September 16, 1999 has been recieved and entered. Amendments to claims 11-14, 17, 19 and 23 have been made and claim 28 has been added. Claims 1-28 are currently pending in the present application.

This application is a 371 national stage filing of PCT/GB98/00468 filed 03/02/98, and claims priority to the foreign application 9704305.3 filed in the United Kingdom, 03/01/97.

Claim Objections

Claims 3-10 are objected to because of the following informalities: The claims as written do not comply with the sequence rules 37C.F.R. 1.821(d). When claims discuss a sequence that is set forth in the "Sequence Listing", reference to the sequence must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 23 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 23 is a directed to a method wherein the system is a transgenic animal. The specification does not define what is specifically meant by a 'system', but from the claim and disclosure it appears that a transgenic animal is intended, and not just cells. In this case, claim 23 encompasses any transgenic animal, including a human being. Changing the claim to read a transgenic non-human animal would obviate this rejection.

Double Patenting

Claims 1-22, 28 are provisionally rejected under the judicially created doctrine of double patenting over claims 55-57 of copending Application No. 09/029,348. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: Application No. 09/029,348 is drawn to a polypeptide comprising a pro-α collagen C-propeptide moiety with specific recognition sequences (claims 40-41, 44-46, 48) and a second moiety containing a triple helix forming domain. Also claimed is the DNA molecule encoding the polypeptides, an expression host cell and a method of producing collagen with said DNA and host cell (claims 55-56). The instant application claims a method of producing a desired procollagen by expressing in a host cell, a gene which encodes a polypeptide

with the same embodiments recited in the claims 39-49 of Application No. 09/029,348. Since the methods to produce the polypeptide in both applications are dependent on the broad claims encompassing any combination of procollagen chains, the claims 54-56 of Application No. 09/029,348 drawn to the polynucleotide encoding the desired procollagen polypeptide, the host cells expressing the polynucleotide and the method to produce a desired procollagen are the same as those recited in claims 1-22, 28 in the present application.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-22, 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a desired procollagen polypeptide in a cell comprising; a) generating a polynucleotide which encodes a pro-α collagen chain

polypeptide with altered selectivity for pro-α chain assembly comprising; i) a first C-terminal propeptide domain from a first pro-α chain type having activity for the assembly into a trimeric procollagen wherein said propeptide contains the recognition sequence GNPELPEDVL DVQLARLRLL SSR; and, ii) a second domain containing a triple helix forming domain from a pro-α chain type different from said first type, b) expressing said polynucleotide in a mammalian cell to produce said pro-α collagen chain polypeptide, and c) allowing said polypeptide assemble into said procollagen, does not reasonably provide enablement for a method of producing a procollagen with other specific recognition sequences other than GNPELPEDVL DVQLARLRLL SSR or in cells other than mammalian cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)).

Nature of the invention. The claims are drawn to a method of producing a desired procollagen in a system wherein assembly of the of the trimeric structure of the collagen molecule is dictated and controlled through the use of C-terminal propetide sequences. Based on previous observations of the assembly of endogenous collagen molecules, a method of domain shuffling is proposed wherein one attaches the C-terminal propeptide of one pro-collagen to the trimeric forming region of another to form a hybrid molecule, wherein the C-terminal propeptide directs nucleation and specific assembly of the hybrid molecules. The novel feature of the present invention is the observation by the Applicant of specific sequence in one C-terminal propeptide,

and based on homology sequences in corresponding procollagen molecules that can be used to direct the nucleation and assembly of the trimeric forming domains of the procollagen molecule. Hybrid molecules can also be used to direct assembly with endogenously expressed host collagen molecules to derive the desired collagen molecules.

Breadth of claims. The claims are broad, encompassing generation any desired collagen molecule or derivative thereof. The breadth of the claims encompass the use of any combination of C-terminal domain with any trimeric forming domain for the assembly of the desired procollagen. This can result in naturally occurring trimeric formation or molecules which can only be assembled through the use of domain shuffling. Further, the breadth of the claims encompass the assembly of trimeric domains of different species through the use of the C-terminal propeptide domain. The recitation of 'derivative thereof' would encompass the assembly of trimeric domains which do not naturally occur and which are created through other molecular manipulations. Finally, the system encompasses the use of any type of cell from any species for the assembly of procollagens from any species.

Guidance in the specification and State of the art. The specification teaches specifically how one C-terminal domain can be used to assemble the trimeric domain of another procollagen molecule. The specification gives specific guidance on how the specific amino acids in the C-terminal domain result in the recited recognition sequence of claim 6 (page 25) and using sequence comparison programs, defines the amino acid of the recognition sequences of other known collagen molecules. However, the specification is silent with respect to example for the

creation of other hybrid procollagens to demonstrate that the general strategy and the proposed recognition sequences of the other procollagen molecules will function as in the single detailed example.

For example, Myllyharju *et al.* detail experiments which demonstrate that expression of hybrid collagen molecules in insect cells. Reviewing previous work, Myllyharju *et al.* teach that human procollagen can assemble in insect cells but is not stable unless human propyl 4-hydroxylase is also expressed (page 21824; middle of second column). Further, co-expression of proα1(I) amd proα2(I) results in human type I procollagen, however,$[proα2(I)]_3$ do not form pages 21824-5; bridging paragraph). Walmsley *et al.* also teach the importance of propyl 4-hydroxylase in the stability and secretion of procollagen molecules (page 14884; summarized in abstract, page 14886; figure 1). Walmsley *et al.* also teach that derivatives of collagen molecules, in this case mini-genes absent of triplex forming regions, can be created and expressed, however the polypeptides encoded by these mini-genes will not assemble in procollagen molecules (page 14891; top of column 2). Therefor, by extension, not all possible derivatives of procollagen can be used to direct the formation of a desired collagen molecule. Applicant has proposed a potential method for the assembly of procollagen molecules, however, because the assembly of collagen is a complex multi-step process, modifications to the endogenous gene may result in modifications which would produce a hybrid molecule incapable of producing the desired collagen.

Amount of experimentation necessary. Applicants have described a potential method for the assembly of desired collagen molecules and prophetic recognition sequences based on computer homology searches, however for the reasons detailed above without the reduction to practice of more than one example, it is not clear if the predicted methodology will be operative for all the different combinations of collagen molecules encompassed in the scope of the claims. Further, Applicants have not addressed the problem of the extensive post-translational modification of collagen molecules and the need of other enzymes, such as the propyl 4-hydroxylase in yeast, to obtain a collagen molecule which would assemble properly, and so have not provided the proper guidance to achieve the proposed method in all types of cells.

In view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue experimentation by one of skill to practice the invention in the breadth in which it is claimed,

Claims 23-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)).

Nature of the invention. The claims are drawn to a method of producing a desired procollagen in a system wherein the system is a transgenic animal or plant comprising the genes of claim 1. The basis of this rejection is not the method of producing the desired procollagen *per se*,

it is the critical feature that a transgenic plant or animal must be created to practice the claimed method as claimed. Read in light of the specification, the animals and plants would serve as the system and as a source of the procollagen.

Breadth of claims. The claims are broad, encompassing generation any transgenic animal and plant comprising expression and assembly of the genes recited in claim 1.

Guidance in the specification. The specification teaches a general method on how to create cell lines which express the desired genes (pages 10-11) and describes a specific example of the creation of pα1(III)and pα2(I) hybrid genes and the expression of said genes in SP cells (pages 17-18). However, the specification is silent with respect to guidance or example for the creation of any transgenic animal or plant. There is no guidance, reference nor art of record to the use of appropriate vectors, the specific procollagen gene sequences and cloning details for all the claimed species, nor operable methods to create any transgenic animal or plant.

Predictability of the art. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). This is particularly true in the art of transgenic animals with respect to transgene behavior. Without evidence to the contrary, transgene expression in different species of transgenic animals is not consistent and varies according to the particular host species. This observation is specifically supported by Hammer *et al.* report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The observation is further supported by Mullins *et al.* who report on

transgenesis in the rat and larger mammals. Mullins *et al.* state that "a given construct may react very differently from one species to another" (page S39, Summary). Wall *et al.* further report that "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies" (page 2215, first paragraph). Since the applicants have not disclosed the nucleic acids encompassed by the claims, there is no way to predict efficiency nor expression of a transgene. With respect to transgenic plants, Ruggiero *et al.* demonstrate that one can express the proalpha1(I) chain in plants, however, it not clear that expression of other procollagen chains, and in particular the hybrid genes recited in the claims, will be expressed, processed and assembled properly in a plant host.

Berg teaches that a single procollagen can be expressed in a transgenic mammal wherein the animal is essentially a bioractor and the collagen produced is assembled and secreted. However, because the specification does not disclose the details of expressing the procollagen chain, the expected effect of introducing the nucleic acid, nor if/what cellular material it expects to modify, the claims encompass changes which may produce an animal which is not viable or incapable of producing progeny. In particular, read in light of the specification, one embodiment is the production of heteromeric collagen chains between species which has presently not been demonstrated in art. As taught in the specification, the proposed mechanism for nucleation and assembly of procollagen chains can be found in the C-terminal propeptide portion of the procollagen chain (pages 27-28; bridging paragraph), however, as demonstrated in Colombatti *et al.* when intact genes for procollagen are expressed in non native host cells, in this case chicken

procollagen in mouse NIH3T3 cells, no self-association was observed for either α1(VI) or α2(VI) (page 785; summarized in abstract) suggesting that not all combinations of procollagen chains will undergo the proper processing and/or assembly in any type of cell. Furthermore, because of the lack of homology of procollagen chains between species, the α1(VI) or α2(VI) from chicken do not form the chimeric chicken/mouse heteromers one expected based on known structures and homology, suggesting further that domain switching between procollagen chains will not result in the formation of any and all combinations of desired procollagen chains (page 785; summarized in abstract).

Amount of experimentation necessary. Applicants have described a prophetic transgenic animal and plant wherein the animal and plant must express, process and assemble a desired collagen. While the methodology to create transgenic mice is routine, the creation of any transgenic animal is not. In particular, no ES cell for animals other than mice exists to date, so the creation of animals which depend on homologous recombination are not enabled in the art. Further, while methods for the introduction of a gene are routine, the expression of the gene and resulting phenotype of the animal is not. Without an actual reduction to practice, it is possible to predict that introduction of a transgene or an alteration to a gene would result a predictable phenotype or even in a viable animal. In this specific case, as suggested by Colombati *et al.* (discussed *supra*) the normal biological function and assembly of intact procollagen chains in unique host cells can not be predicted simply by homology or known structure. Further

alterations in expression and the effect of domain swapping of procollagen genes can not even be predicted in a transgenic animal and plant.

In view of the of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required one of skill in the art undue experimentation to practice the invention as claimed.

Claims 26 and 27 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)).

Nature of the invention. The claims are drawn to a method of producing a desired procollagen in a system wherein the system is a transgenic animal or human in need of gene therapy comprising the expression of the genes of claim 1. The basis of this rejection is not the method of producing the desired procollagen *per se*, it is the critical feature that to practice the claimed method one must perform methods of gene therapy. Read in light of the specification, treatment for osteogensis imperfecta, Ehlers-Danlos syndrome or chrondrodysplasia may be obtained by the expression of the appropriate desired collagen (pages 11-12; bridging paragraph).

Breadth of claims. The claims are drawn to treating or preventing either osteogensis imperfecta, Ehlers-Danlos syndrome or chrondrodysplasia, which are known genetic disorders associated with cmutations in the collagen gene. It is not clear what is meant by in need of,

however, in the broadest interpretation this could be in need of gene therapy for diseases. No specific method steps are recited in the claim, nor is specific guidance given in the specification, so the delivery of the DNA to any cell can be achieved by any means.

Guidance in the specification. The specification is silent with respect to methods of gene therapy. the specification does not give specific guidance regarding the amount of expression needed to obtain amounts of the target gene necessary for a therapeutic effect. It does not recite amounts or routes of administration of the ligand for target gene expression.

State of the prior art. At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by two subsequently published reviews. Verma et al. teach that as of 1997, "there is still no single outcome that we can point to as a success story" (p.239, col. 1). The authors go on to state, "Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (p. 239, col. 3). Anderson states that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease" (p. 25, col 1) and concludes, "Several major deficiencies still exist including poor delivery system, both viral and no-viral, and poor gene expression after genes are delivered" (p. 30).

Predictability of the art. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). Since the applicants have not described or provided examples of how their methods differ from those presently found in the art, and in great part rely on the methods of gene delivery established by others, Applicants face the same shortcomings faced by

others skilled in the art with regards to the specificity of cell targeting and the ability to tightly regulate gene expression. Further, as discussed *supra* for the 112 rejections of claims 23-26, neither the behavior of native nor hybrid procollagen genes expressed in cell lines can be predicted based on homology or known structure. In view of the lack of guidance in the specification, and if one could overcome the technical hurdles presently encountered in practicing gene therapy, it is unclear which hybrid procollagen chains would be needed for the successful treatment of the recited disease. As suggested above, and in light of the fact that the therapeutic amounts of target genes has not been established, it is unclear that these systems can be regulated *in vivo* in a way to produce therapeutic amounts of target gene product. This is further complicated if treatment is dependent on the introduction of more than one DNA construct for the production of more than one procollagen chain. As suggested above, the delivery and expression of one construct faces several problems, the need to deliver more than one DNA construct to a single cell to establish a working system which results in a therapeutic effect poses an even greater hurdle.

Amount of experimentation necessary. Besides the general expectation that it will require years of further research to develop effective gene therapy (Anderson, p.30), it would require extensive research to understand the fundamental biology of the system. Applicants have described a method for a potential use of hybrid procollagen chains, but essentially all of the work required to ultimately develop therapeutic methods has been left for others.

For reasons discussed above, it would require undue experimentation for one of ordinary skill in the art to use the invention in the breadth in which it is claimed.

Written Description

Claims 23-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is referred to the interim guidelines on written description published on December 12, 1999 in the Federal Register at Volume 64, Number 244, pp.71427-71440.

Claims 23-26 are drawn to a transgenic non-human animal wherein said transgenic animal one or more cells of the animal contains the nucleic acid of claim 1. The breadth of this claim would encompass transgenic and knockout type technologies, as well as chimeric animals. The specification recites general methodology one can use to create a transgenic animal (pages 84-87), however, there is no reduction to practice of any transgenic animal in the specification, nor the use of the construct to create a cell which could give rise to a transgenic mouse or any other animal. Further, no examples using ES cells are described to demonstrate that cell lines or that animals can be created which have undergone homologous recombination. The art indicates that there are multiple and different obstacles in creating transgenic animals of different species, among these are substantial variation among animals in transgene expression and variation in transgene effect due to species variation of the gene product produced.

In analyzing whether the written description requirement is met for genus claims, it is first determined were a representative number of species have been described by the complete

structure. (It is not realistic to expect that the "complete structure" of a mouse, or any other animal could be described. Therefore the inquiry required by this portion of the written description guidelines is interpret to be whether the phenotypic consequences of altering a the genotype have been described). In this case, the few disclosed embodiments are not representative of the enormous number of products claimed. The claims encompass any animal, with an isolated nucleic acid encoding the desired procollagen recited in claim 1. Further, since expression of the transgene can be operably linked to any promoter, the claimed genus encompasses many more possible species. This includes the collagen gene expressed as a transgene under the control of a heterologous promoter or an altered endogenous collagen gene created though homologous recombination. The specification does not disclose examples of any animal created with a collagen transgene construct, nor does it predict or describe how an alteration in the gene expression would affect the phenotype of the animal generated. Without even a function described for the endogenous gene, it is unclear what effect an alteration in the gene would result. Further, since only one or more cells must contain the nucleic acid, the phenotype of the chimeric animal encompassed by the claim may vary from animal to animal because of the location, type or number of cells in the animal which contains the transgene.

Next, it is to be determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. It is not possible to adequately describe the claimed products because the effects of expression of a heterologous gene can not be predicted. This is particularly true in the art of transgenic animals with respect to transgene

behavior. Without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not consistent and varies according to the particular host species. This observation is specifically supported by Hammer *et al.* who report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The specification does not disclose an expected phenotype of the transgenic animal, as discussed *supra*, Colombati *et al.* teach collagen is a diverse family of proteins with diverse biological functions and expression patterns *in vivo*. The specification has defined a potential method to obtain a desired collagen, but has not demonstrated a specific biological function, nor predicted a specific function with which one could describe the phenotype of a transgenic animal expressing said nucleic acid, or if the expression of one transgene would result in the desired collagen due to the expression of endogenous host collagens. Since the transgenic, knock-out and chimeric animals are encompassed in the claims, many different potential phenotypes are possible for each of these transgenic animals. Further, even if the same nucleic acid is used in the transgene construct for the desired collagen, the type of promoter and site of insertion into the host genome will affect transcription of the transgene thus potentially resulting in phenotypically different animals. The limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the huge genus recited in the claims at the time of the application was filed. Thus the Applicant was not in possession of the genus of all transgenic animals which contain a polynucleotide with a

desired collagen nucleic acid, and is concluded that the written description requirement is not satisfied for the claimed genus.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claims 1, 11-14 are vague and unclear in the recitation of 'or derivative thereof' because it is not clear how similar or different something must be to be defined as a 'derivative'. Since the term derivative is not defined by some distinguishing feature or % homology the metes and bounds can not be determined.

Claims 12 are unclear in the recitation of 'encodes', because it is not clear if what is meant is to produce a protein from the transgene construct, or that the transgene produces no protein, however, the polynucleotide sequence has an open reading frame which code for a protein.

Claim 26 is not clear if the human is the transgenic animal, or that the system is a transgenic animal **or** a human, also are both the transgenic animal and human in need of gene therapy or only the human?. Further, the metes and bounds of what constitutes an individual that "**is in need** of gene therapy" are vague and unclear.

Claims 1-27 are incomplete because they recite a method for producing a desired procollagen in a system, but does not recite any method steps to this end only enbodiments of the desired procollagen or system.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 2, 6 and 11-22 are rejected under 35 U.S.C. 102(a) and 35 U.S.C. 102(e) as being anticipated by Prockop *et al.*

Claims 1, 2, 6 and 11-22 encompass a method of producing a desired procollagen by creating recombinant pro-α collagen polypeptides wherein the pro-α collagen polypeptide comprises a C-terminal propeptide containing the recognition sequence of one type of pro-collagen (specifically GNPELPEDVL DVQLARLRLL SSR of claim 6) and another portion of a second type of pro-collagen wherein said polypeptide is encoded by a gene in a system, wherein the system is a yeast, insect or mammalian cell. Prockop *et al.* teach hybrid pro-collagen genes

which encode hybrid polypeptides (column 2; lines 25-57), specifically, the 5' COL1A1 encoding a portion of the pro-α1 type I chain is linked to the COL2A1 gene which encodes the pro-α1 type III chain. Further, Prockop *et al.* provide the guidance and teach the necessary steps for a method in which the recombinant procollagen polynucleotides can be expressed in yeast (columns 12-14; Examples 8-9), insect cells (columns 10-12; Example 7) and mammalian cells (column 7-10; Examples 1-6) to produce the desired pro-α collagen chains and/or assembled procollagen in these cells. Finally, Prockop *et al.* specifically teach that one can express multiple copies of the gene and that one can engineer sites to produce "desired regions of procollagen or collagen" (column 10; lines 52-56). The recognition sequence recited in claim 6 of the present application is the same sequence present in COL2A1 gene which encodes the pro-α1 type III chain taught in Prockop *et al.* Embodiments encompassed in claims 11-16 are taught throughout the specification in particular at column 10; lines 52-56. Prockop *et al.* teach one can use the hybrid genes in several types of cells to produce the desired collagen, therefor, Prockop *et al.* anticipate the claimed invention.

Claims 1-22, 28 are provisionally rejected under 35 U.S.C. 102(e) as being anticipated by copending Application No.09/029,348 which has a common inventor with the instant application.

Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e), if patented. This provisional rejection under 35 U.S.C. 102(e) is based upon a presumption of future patenting of the copending application.

This provisional rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

This rejection may not be overcome by the filing of a terminal disclaimer. See *In re Bartfeld*, 925 F.2d 1450, 17 USPQ2d 1885 (Fed. Cir. 1991).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach, whose telephone number is (703) 305-3732. The examiner can normally be reached on Monday through Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examine by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on (703) 308-2035. The fax number for group 1600 is 1(703)308-4242.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is (703) 308-0196.

Joseph T. Woitachh

JASEMINE CHAMBERS
SUPERVISORY PATENT EXAMINER
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